

Hetero-Polypentotide Duplex as a Pre-RNA Replicator: Origin of Non-Local Order

by

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D-Ribulose-1,5-bis-phosphate self-interacts with a counter-oriented molecule of the 2-ketopentol and, by extension, forms a homo-polypentotide duplex with complementary, H-bonded, anti-parallel (C1-C5:C5-C1) strands. Inclusion of a second pentose species allows formation of a complex sequence encoding a functional structure, illustrated with a model aminoacyl-synthetase. D-3-Keto-ribulose, β -D-ribulofuranose, and β -D-ribofuranose also self-interact, analogous to D-ribulose, providing alternative strand-binders. D-ribose-1,5-bis-phosphate does not self-interact; the aldopentose yields instead a potential spacer between binders. A hetero-polypentotide duplex containing anti-parallel strands with a complex, complementary sequence duplicates, in simple form, structural features of an RNA molecule, whose D-ribofuranose-phosphate scaffold monomers derive from D-ribulose-phosphate, produced by an autocatalytic sugar-phosphate cycle. This supports the proposition that the polynucleotide double-helix evolved from a polypentotide ladder-like replicator, retained as its nucleobase scaffold. Simple formose intermediates and an invariant phosphate within the sugar-phosphate cycle conforms with early sugar attachment to a surface-bound polyphosphate chain. A specific triose distribution along a polyphosphate chain could double with poly(D-ribulose-1,5-bis-phosphate) separation into two poly(triose-phosphate) strands. Path analysis and supporting set of reactions identify this reaction as the likely origin of template-directed propagation of non-local order. Selective amplification of variant sugar-polyphosphate sequences that optimally damped the statistical thermodynamic forces driving propagation, opened the way for new life on Earth.

Key words: *sugar-phosphate replicator; stable variants, double-helix scaffold; origin of life*
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Invariants characterizing intermediates in central metabolism and pathways of amino acid and nucleobase synthesis were recently identified as former attachment sites for distant, pre-RNA polymers (Davis, 2012, 2013ab, 2015). This interpretation was motivated by results from an earlier series of investigations that linked genetic code evolution to the growth of amino acid synthesis pathways (Davis, 1999a, 2002, 2007, 2008a). The ubiquity of a free carboxyl group among amino acid intermediates was found to conform with initial attachment to dual function cofactor/adaptor tRNA. Diversification of tRNA species coordinated the synthesis of new amino acids with codon recruitment, in the pre-LUCA¹ era (Davis, 2008b, 2009, 2011, 2013c). In addition to their invariants, the reductive pentose cycle (RPC) and reductive citrate cycle (RCC) reaction sequences have the form of autocatalytic processes (Wächtershäuser, 1988, 1992). When considered together with the dependence of ribozyme catalyzed reactions on their sugar-phosphate (carbotide) moiety (Sgrinani and Magistrato, 2012; Sponer et al., 2012), the RPC and RCC appear to have been replication cycles, as anticipated by Orgel (2008), in a pre-RNA, polycarbotide era (Davis, 2015).

Self-interacting, self-annealing pre-RNA polymers, furthermore, were found to circumvent (Davis, 2015) thermodynamic and kinetic constraints (DeDuke and Miller, 1991) on *de novo* formation of a 2-dimensional, archiac metabolic network at a positively-charged mineral surface (Wächtershäuser, 1988; 1992). Early reduction from 3-dimensional processes, in an aqueous medium, to a 1-dimensional, surface-bound polymeric replicator thus appeared likely. The prospect of replication evolving directly from a spontaneously formed 2-carbon sugar, glycoaldehyde, produced by the autocatalytic formose cycle (Butelrow, 1861; Breslow, 1959; Benner et al., 2010) would, likewise, have been impeded by stereochemically unconstrained molecular interactions, at a pre-catalyst stage.

A polypentotide ladder-like duplex, containing keto-pentol and aldo-pentol self-interaction

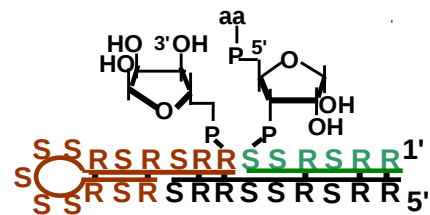
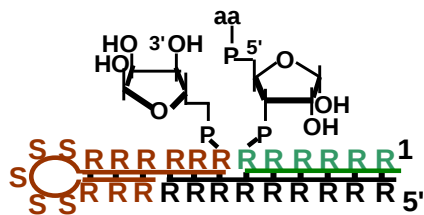
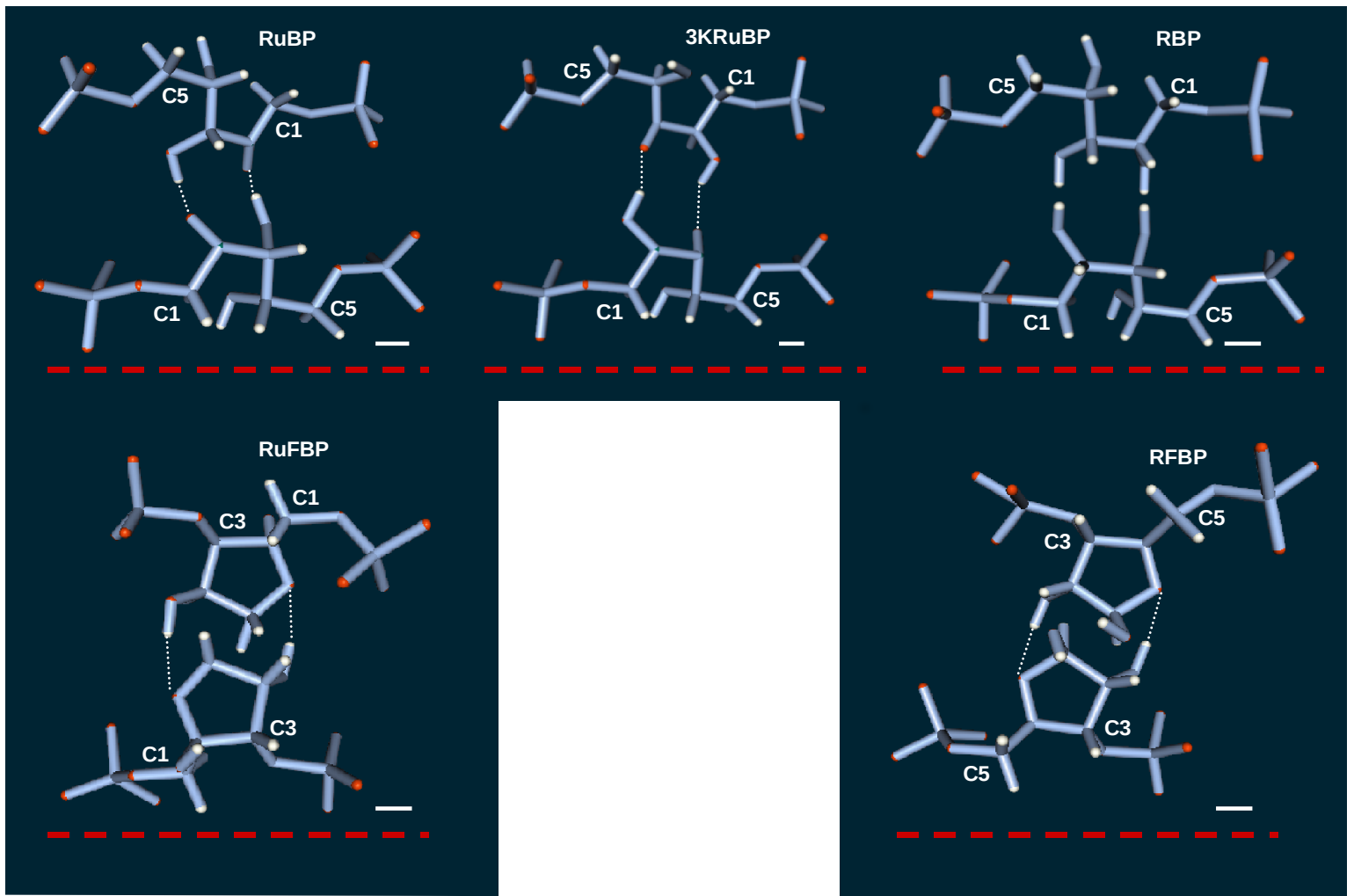
¹ LUCA, Last Universal Common Ancestor.

pairs is described here. The duplex has the capacity to form a non-periodic sequence of H-bonded monomers within anti-parallel strands, comparable to an RNA double-helix. Its significance with respect to the transition from spontaneous, autocatalytic sugar-phosphate synthesis to template-directed polymerization is considered in relation to the origin of life, particularly with respect to biopolymer acquisition of non-local order².

Mixed orientations (1-5/5-1) of phosphorylated ribulose monomers were previously used to construct models of a poly(ribulose-phosphate) duplex with complex complementary strands (Davis, 2015). The 2-ketopentol forms O2..H-O3 and O3-H..O2 bonds with a counter-oriented ribulose molecule in the duplex. By forming H-bonded complementary monomer strands, the pre-RNA polypentotide duplex incorporates, in a simple form, a fundamental feature of an RNA double-helix. Given monomers in the poly(ribose-phosphate) scaffold of RNA derive from ribulose-5-phosphate, a polypentotide replicator was inferred from this to have preceded the polynucleotide double-helix.

Figure 1 – Self-interactions between counter-oriented pentose-phosphate pairs attributed to a surface-bound polypentotide. RuBP, D-ribulose-1,5-bis-phosphate pair forms O2..H-O3 and O3-H..2 bonds (dotted lines). 3KRuBP, D-3-keto-ribulose-1,5,bis-phosphate can form O2-H..3O and O3..H-O2 bonds. RBP, D-ribose-1,5-bis-phosphate has hydroxyl groups at both interaction sites (C2, C3), yielding a non-interacting, space-filling pair. RuFBP, β-D-ribulofuranose-1,3-bis-phosphate can form H-bonds at O2..H-O4 and O4-H..O2, producing a self-interacting pair. RFBP, β-D-ribofuranose-3,5-bis-phosphate could form H-bonds at O4..H-2O and O2-H..O4, resulting in another self-interacting pair. Blank space, no furanose can form from 3-keto-ribulose. Diagrams show simple and complex sequence polypentotide models of the Tamura-Schimmel aminoacyl-synthetase ribozyme. R, ribulose-phosphate monomer (binder); S, ribose-phosphate monomer (spacer). Brown, minihelix; black, bridging strand; and, green, donor strand; aa, amino acid. ■■■■■, signifies a cationic mineral surface; bar, 1 Å. Each pair was constructed with Facio 20.18 molecular model building software (Suenaga, 2005) and optimized using Gamess, 18 Aug 2016 version (Schmidt et al. 1993).

² Molecular order not attributable to existing atomic bonds: a virus RNA retains the same number of H-bonds and phosphodiester-bonds, after inactivation by a base-pair permutation, indicative of non-local order. Complexity quantitates the aperiodicity present in non-local order.



Replacing mixed, intra-strand pentose orientations, as the source of sequence complexity, by incorporation of a second pentose species, yields an additional RNA feature: anti-parallel strands; where monomers have identical intra-strand orientation and opposite inter-strand

orientation. When copolymerized with ribulose, 3-keto-ribulose (Fig. 1, 3KRuBP), with reverse ketone and hydroxyl groups in the ribulose self-interaction site (Fig. 1, RuBP), a polypentotide duplex results possessing complementary binary sequences. Under anoxic early Earth conditions, 3-keto-ribulose stability (Sera, 1962; Ivlev and Dubinsky, 2011) may have permitted replication and sequence propagation. As ribose-phosphate monomers (Fig. 1, RBP) lack a proton acceptor, they cannot self-interact. These pairs could, however, act as space-fillers and align self-interacting pentoses within a sequence. In this way, ribose pairs provide an embedded sequence scaffold. Its presence as an external scaffold in a polynucleotide double-helix, would then be a refinement of its earlier role. β -D-Ribofuranose-3,5-bis-phosphate forms (Fig. 1, RFBP) inter-strand O4..H-O2 and O2-H..O4 H-bonds (Desiraju and Steiner, 2001). Ribulofuranose-3,1-bis-phosphate (Fig. 1, RuFBP) also forms O2..H-O4, O4-H..O2 H-bonds on its C2:C4 edge. Discounting 3-keto-ribulose, which cannot fold into a furan ring, there are open- and closed-form pentoses that could copolymerize into a complex sequence, capable of encoding a function promoting self-propagation.

Models of a ribozymal³ aminoacyl-RNA synthetase (Tamura and Schimmel, 2006) are shown in Fig. 1. They replace RNA with anti-parallel 1-5:5-1 double-strand polypentose chains. Counter-oriented, self-interacting ribulose-pairs (binders) and non-interacting ribose-pairs (spacers) form the proposed carbozymes. Each contains three strands, as in the ribozyme: an amino acid donor strand, a recipient mini-helix, and bridging strand, with 7, 14, and 9 pentose monomers, respectively. Monomers outside the charging site are open-form pentoses linked by intra-strand phosphate bonds (C1-PO₄-C5). Within the charging site are ribofuranoses, at the C1 mini-helix and C5 donor-strand terminus. With 12 binder pairs and 5 spacer block, forming its single loop, the left model maximizes carbozyme simplicity and stability. Its long, repetitious binder sequence; however, would elevate the risk of error,

³ 2'-deoxy-nucleotides formed the donor strand in the Tamura-Schimmel synthetase.

through misalignment by self-annealing, or binding to another copy of the carbozyme. In the right-hand model, 5 spacers are interspersed among 7 binders in the hairpin 'stem sequence'. This sequence is one of 792 ($12!/(7!5!)$) different pair arrangements. Its complexity reduces the risk of mispairing within, and between, model carbozymes.

Monomer sequence complexity is a feature of all self-replicators. As an asymmetry within an ordered state of matter, sequence complexity differentiates life from other ordered physical states (Schrodinger, 1943). The departure from familiar ordered states, exemplified by a crystal lattice, reflects a restriction on the range of the molecular forces producing order. After binding forces initially position a monomer on the template surface, in template-directed polymerization, chain-extension follows with covalent-bond formation: specifically, through H-bond and phosphodiester bond formation. A semi-crystalline macromolecule results, bearing a template-imprinted, 1-dimensional monomer-order. The resulting sequence is invariably an aperiodic ordered state of matter in all known life forms. This contrasts with the simple, periodic 3-dimensional lattice, produced by binding forces acting in 3-dimensions during crystallization.

Being template-derived, the sequence complexity corresponding to asymmetry within an ordered polymer strand, and based, for example, on nearest-neighbor monomer frequencies, has no effect on the binding and extension reactions. Thermodynamic equilibrium in template-directed polymerization is, consequently, independent of template sequence complexity: a simple periodic sequence of monomers being equivalent, from the standpoint of replication reaction thermodynamics, to an aperiodic arrangement, with high sequence complexity (Davis, 1965, 1995a). Genomic complexity can be viewed, therefore, as a product of thermodynamic freedom associated with the monomer-pair stacking order in replication.

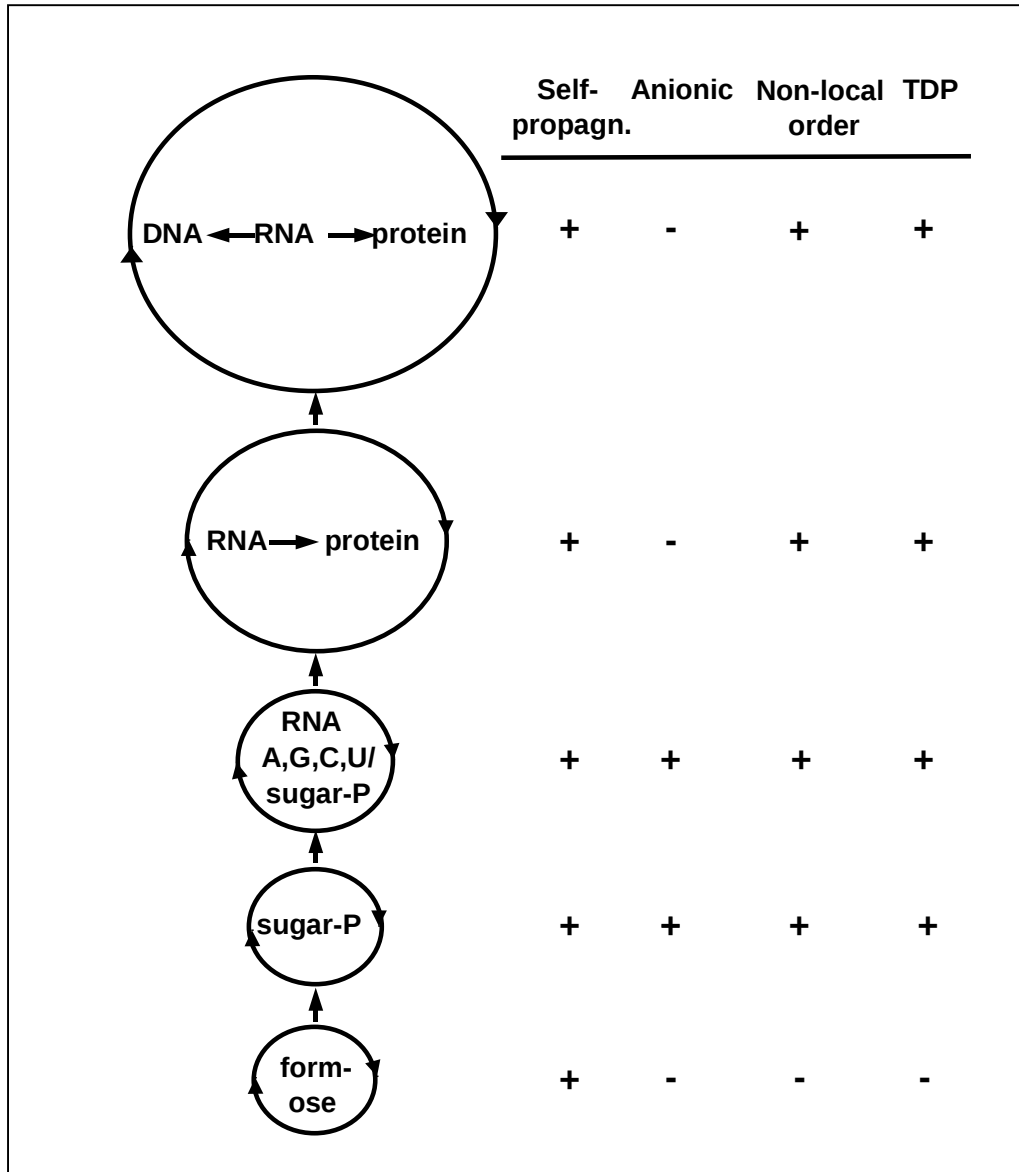
In compliance with Curie's symmetry principle, encoded sequence complexity demonstrably exceeded structural complexity, in an analysis of complexity levels within gene

and protein monomer sequences, polypeptide-chain torsion angles, and substrate molecule (Davis, 1974). Selective amplification of variant sequences, formed through chance events, that optimally damped the statistical thermodynamic forces promoting propagation (Davis, 1996, 1998, 2000), have produced substantial increases in encoded, non-local order.

Accompanying increases in structural and functional complexity resulted from the capacity to form a stable variants. This reflects the fact that once locked into a template, non-local order remains unaltered, discounting occurrence of another mutation and the rise, or fall, of frequency in response to changes in the physicochemical forces responsible for evolution.

A hetero-polypentotide duplex with anti-parallel strands of complementary, H-bonded monomer sequences, suitable for replication, plainly supports occurrence of pre-RNA template-directed polymerization. This points to an era, centered on the RPC, or antecedent sugar-phosphate cycle, as the site of origin of template-directed polymerization (Fig. 2). In addition to being an RPC component and strand-binder in a polypentotide replicator (Fig. 1), ribulose-5-phosphate is precursor to ribose-5-phosphate monomers in the RNA polypentotide scaffold. It thereby links the sugar-phosphate cycle to emergence of the RNA era (Fig. 2); a transition shifting non-local order away from reactive carbohydrates to more

Figure 2. Initial auto-catalytic, sugar-generating reaction and set of increasingly advanced self-propagating polymers with inferred occurrence of 'non-local order' and related attributes in the proposed 'origin of life' scenario. In ascending order they are: formose reaction, sugar-phosphate cycle, RNA era, 'RNA/RNA-derived protein' (genetic code/cell division stage), 'RNA/RNA-derived protein/RNA-derived DNA' (pre-LUCA stage and beyond). The hetero-polypentotide model implies TDP preceded RNA, placing the transmission of 'non-local order' before RNA, in the sugar-P era: poly(sugar-P) duplex with parallel poly(P) scaffolds, and binary (pentose, P) sequence, split into poly(triose, P) strands, following CO₂ fixation. +, present; -, absent or non-obligatory; TDP, template-directed polymerization; A, adenosine; G, guanosine; C, cytosine; U, uracil; P, phosphate group.



stable nucleobases. Ribulose, in the form of poly(ribulose-1,5-bis-phosphate), is the replicative-form of poly(glycerate-3-phosphate), whose monomers yield glyceraldehyde-3-phosphate - an RPC component and phosphorylated derivative of a formose cycle reactant (Davis 2012, 2013, 2015). Hence, it contributes to the synthesis of the formose carbohydrate, and 'autocatalyst', glycoaldehyde.

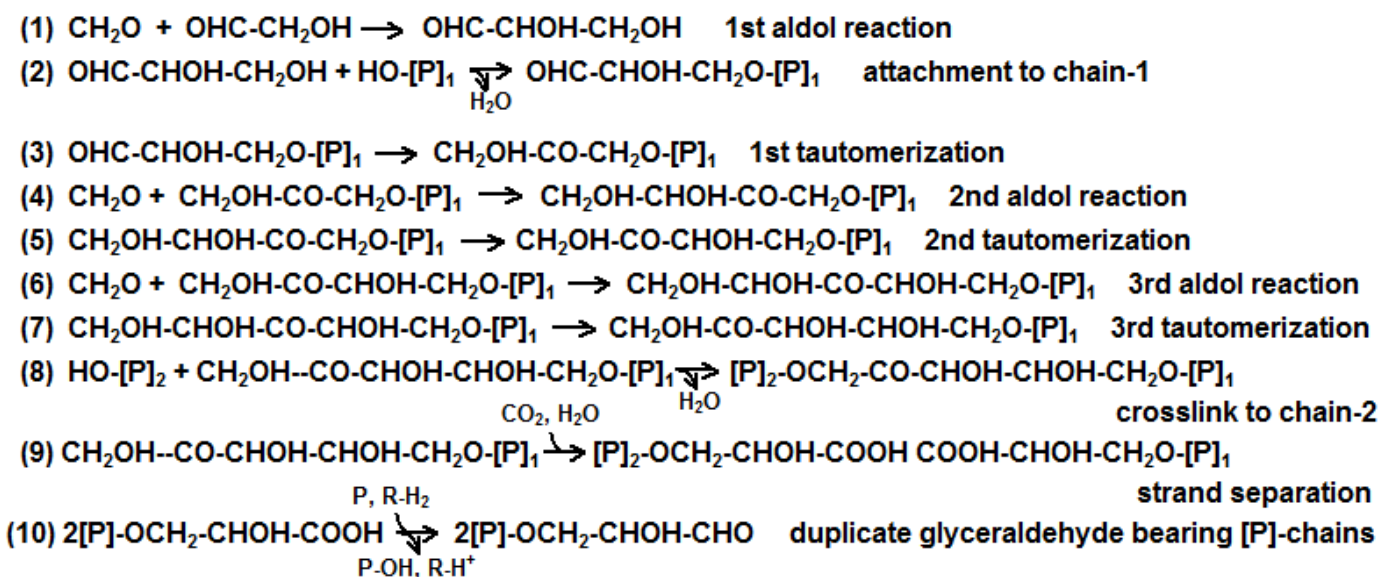
Polyphosphate participation, at the origin of life, in providing a molecular framework and energy source was formerly suggested by Brown and Kornberg (2004) and Achbergerova

and Nahalka (2011). An initially random distribution of sugar molecules along a surface-bound, inorganic polyphosphate chain could be anticipated to evolve toward the optimal sugar distribution through repeated strand-doubling (Davis, 2013b, Fig. 5a). Cleavage of ribulose-1,5-bis-phosphate, on carboxylation and hydrolysis, in the autocatalytic sugar-phosphate cycle achieves this. The sugar-phosphate cycle thus emerges as pivotal in the origin of life. It is seen to convert a 3-carbon, phosphorylated derivative of the autocatalytic formose reaction cycle, able to generate multiple carbohydrate-forming side-paths (Benner et al. 2010), to a polypentotide and, subsequently, poly(nucleobase-pentotide) replicator.

Formation of stable variants allows a replicator to evolve; lowering the effective activation barrier to propagation, or recruiting new sources of free energy to drive propagation (Davis, 1996, 1998). Lacking non-local order, reactants in standard autocatalysis cannot explore new reaction paths that require stable variants. Unlike standard reactions, autocatalytic reactions, including polymer replication, characteristically accelerate with reaction advancement (Davis, 1996). In addition, sugar-phosphate and RNA era polymers were polyanionic (Fig. 2), allowing attachment, through charge-attraction, to a cationic mineral surface. Intra-polymer binding interactions would permit polymers, of both eras, to self-anneal and avoid surface entrapment, in a process familiar from competitive replication among midi-RNA in the Q β replicase system (Davis, 1995b, 1995c). Self-interactions also allow cis-acting polymer reactions, including their catalysis (Davis, 2015). Avoiding impediments to surface metabolism foreseen by de Duve and Miller (1991), in this manner, helps explain the extensive reliance on surface-bound polymers in the origin of life, apparent from the prevalence and nature of invariants within archaic metabolic pathways (Davis, 2013c).

Reactions depicting the formation of simple sugars, their incorporation into a poly(sugar-phosphate) duplex, and subsequent separation into two poly(triose-phosphate) chains

appear in the ensuing equations. Equations (1) to (7) contain spontaneous formose reactions (Breslow, 1959; Benner et al., 2010) used to form a pentotide, from glycoaldehyde, that is bonded, after step 2, to a polyphosphate chain. A poly(sugar-phosphate) duplex formed in Eqn. (8) separates into two strands in Eqn. (9) This occurs through formation of a labile intermediate (2-carboxy-3-keto-arabinitol), upon CO₂-fixation. It is familiar from the sugar-phosphate cycle. Moreover, molecular mechanics indicates the reaction to be energetically possible, in the absence of its light-phase catalyst: ribulose-1,5-bisphosphate-carboxylase-oxidase (Rzepa, 2015). Terminal phosphates, [P], were found to facilitate the reaction.



Glycerate conversion to glyceraldehyde completes duplication of the initial glyceraldehyde-[P] molecule (Eqn. 1). This step proceeds via phosphorylation and reduction, in the sugar-phosphate cycle, and analogous reactions likely preceded these known steps. A retro-aldol reaction, as in the formose conversion of aldotetrose to two 2-C glycoaldehyde molecules, may provide an alternative route to triose-[P] duplication. Duplex formation through cross-

linking reactions, within a looped single poly[P] chain, could conceivably assist in preserving colinearity within a binary (sugar, P) sequence.

With distinct triose distributions on poly[P] chains exhibiting different rates of duplication, for reasons noted in connection with self-interactions, the mean rate of propagation (linear kinetics), or threshold for coexistence (non-linear kinetics), could be anticipated to increase over time (Davis, 2000). The thermodynamic and kinetic forces driving spontaneous formation of the triose, and its bonding to a polyphosphate chain, accordingly, generate non-local order. Formation of stable variant sequences allows non-local order to accumulate and more effectively dissipate the physicochemical forces advancing propagation.

The dependence on polyanionic polymers evidently ceased with appearance of proteins, involving RNA-translation (Fig. 2). From pre-LUCA protein residue profiles (Davis, 2002), formation of a fluid-mosaic cell membrane, signaling an end to surface-based metabolism, had completed, when the genetic code was mid-stage (Davis, 1999, 2002, 2006)⁴. In accord with this estimate, a 23-residue low-potential ferredoxin (Davis, 2002), reconstructed by Nørgaard et al., (2009), contained a 6 residue polyanionic N-terminus, suitable for anchoring the protein to a positively charged surface, and code age (stage-5) estimated to predate the cell membrane. By comparison, the earliest sequence in a H⁺-ATPase was an 11 residue proteolipid helix-1 segment of this trans-membrane protein, and it possessed a stage-7 residue profile with no anionic residues. While the transition to a DNA genome (Fig. 2) began before completion of the genetic code (Davis, 2002), heterogeneity between bacteria and archaea/eukaryote DNA polymerase indicates that the transition was not completed until after species divergence (Davis, 1999b; Leipe et al., 1999). Late acquisition of double-strand DNA and evidence that LUCA was a thermophile (Weiss et al., 2016) indicates that ribose lability

⁴ Fourteen stages occur in code formation, based on path-distance in amino acid synthesis. There are three stages in terms of codon base recruitment.

(Larralde et al., 1995) influenced the direction of evolution, at about the time of species divergence, opening the way for genomes with large quantities of non-local order.

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